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(全 3 頁)

⑭5—トリフルオロメチル—2—ピリドン誘導体

⑳特　　願 昭54—32068
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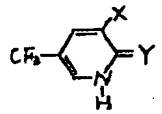
明　細　書

1. 発明の名称　5—トリフルオロメチル—2—ピリドン誘導体

2. 特許請求の範囲

1. 一般式

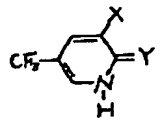


(式中Xは水素原子又はハロゲン原子であり、Yは酸素原子又はイオウ原子である。但し、Xが水素原子の場合、Yはイオウ原子である。)で表わされる5—トリフルオロメチル—2—ピリドン誘導体。

3. 発明の詳細な説明

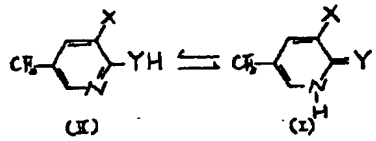
本発明は医薬、農薬、染料などの中間原料として有用で、新規な5—トリフルオロメチル—2—ピリドン誘導体に関する。

詳しくは本発明は一般式

 　(I)

(式中Xは水素原子又はハロゲン原子であり、Yは酸素原子又はイオウ原子である。但し、Xが水素原子の場合、Yはイオウ原子である。)で表わされる5—トリフルオロメチル—2—ピリドン誘導体である。

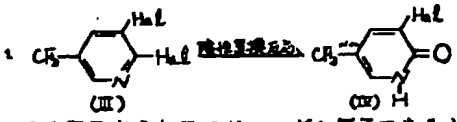
前記一般式(I)の5—トリフルオロメチル—2—ピリドン誘導体は、次に示すような互変異性として存在することができる。


(II)　(I)

(式中X及びYは前述の通りである)

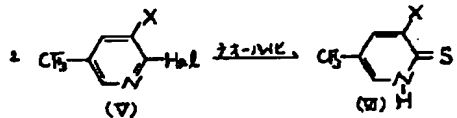
前記一般式(I)において、Xで表わされるハロゲン原子としては弗素、塩素、臭素、沃素が挙げられる。

本発明の5－トリフルオロメチル－2－ピリドン誘導体は通常、例えば下記方法によって製造される。



（上記反応式中 Hal は ハロゲン原子である）

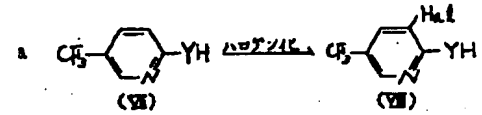
一般に上記反応はジメチルスルホキシド、ジメチルホルムアミドなどの非プロトン性極性溶媒中、水酸化ナトリウム、水酸化カリウムなどのアルカリ水溶液を用いて50～150℃、0.1～10時間で行なわれる。



（上記反応式中X及び Hal は前述の通りである）

一般に上記反応はメタノール、エタノールなどのアルコール類、ジメチルスルホキシド、ジメチルホルムアミドなどの非プロトン性極性溶

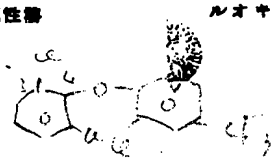
媒などの溶媒中、チオ尿素、硫化ソーダ、チオ硫酸ソーダ、N,N－ジメチルジチオカルバミン酸ソーダなどのチオール化剤を用いて50～還流温度0.5～10時間で行なわれる。



（上記反応式中Y及び Hal は前述の通りである）

一般に上記反応は四塩化炭素、クロロホルム、酢酸、二硫化炭素、水、非プロトン性極性溶媒などの溶媒中、塩素ガス、臭素、チオニルクロライド、スルフリルクロライドなどのハロゲン化剤を用いて0～100℃、0.5～10時間で行なわれる。

本発明化合物は、例えばハロゲン化ニトロベンゼン類と縮合させて4－（5－トリフルオロメチルピリジン－2－イルオキシ）ニトロベンゼン類を生成させ、これを還元して得られる4－（5－トリフルオロメチルピリジン－2－イルオキシ）アニリン類とベンゾイルイソシアネ



ート類とを反応させることによりN－ベンゾイル－N'－〔4－（5－トリフルオロメチルピリジン－2－イルオキシ）フェニル〕ウレア系化合物に誘導できる。詳しくは本発明化合物の3－クロロ－5－トリフルオロメチル－2－ピリドンと3,4,5－トリクロロニトロベンゼンとを縮合、還元して3,5－ジクロロ－4－（3－クロロ－5－トリフルオロメチルピリジン－2－イルオキシ）アニリンを得、更にこのものと2,6－ジフルオロベンゾイルイソシアネートとを反応させると、N－（2,6－ジフルオロベンゾイル）－N'－〔3,5－ジクロロ－4－（3－クロロ－5－トリフルオロメチルピリジン－2－イルオキシ）フェニル〕ウレアを得ることができる。このものは殺虫剤の有効成分として優れた活性を示し、種々の有害虫、特に有害昆虫の防除に有効であって、例えばこの化合物100 ppm水分散液にキャベツの葉片を浸漬し、それを風乾してそこへ2～3令のコナガの幼虫を放ち、8日目に生死を判定した結果、100%の

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死虫率が得られた。

次に本発明化合物の具体的合成例を記載する。

合成例1　3－クロロ－5－トリフルオロメチル－2－ピリドン

〔A〕

5－トリフルオロメチル－2－ピリドン0.2gをクロロホルム20mlに溶解させ、50℃に加温して塩素ガスを1時間撹拌下に通じた。反応終了後、クロロホルムを留去し、トルエン－n－ヘキサンの混合溶媒で再結晶して融点144～147℃の目的物0.15gを得た。

〔B〕

水酸化ナトリウム24gを水125mlに溶解させた水溶液に2,3－ジクロロ－5－トリフルオロメチルピリジン4gを加え、更にジメチルスルホキシド125mlを加えて加熱し、110℃で1時間撹拌下に反応させた。反応終了後生成物を放冷し、希塩酸で酸性にして沈殿物を　、このものを濾過して目的　25

グを　た。

合成例２　５－トリフルオロメチル－２－チオピリドン

２－クロロ－５－トリフルオロメチルピリジン４グとチオ尿素１６７グとをエタノール３０mlに溶解させ、加熱して還流状態で３時間撹拌下に反応させた。その後、水酸化カリウム水溶液１２３グを徐々に加えて還流状態で１時間反応させた。反応終了後、生成物を放冷し、希アルカリ水溶液中に投入して塩化メチレンで洗浄し、酢酸で酸性にした。次いで、塩化メチレンで抽出し、抽出層を水洗後無水硫酸ナトリウムで乾燥させ、塩化メチレンを留去して融点１４７～１５０℃の目的物２１グを得た。

合成例３　３－ブロモ－５－トリフルオロメチル－２－ピリドン

５－トリフルオロメチル－２－ピリドン０.４グを酢酸１０mlに溶解させ、そこへ臭素０.４グを加えて撹拌下で４時間反応させた。反応終了後、酢酸を留去し、塩化メチレン－ｎ－ヘキサンの混合溶媒で再結晶して融点162～165℃の目的物０.４５グ　　た。

合成例４　３－クロロ－５－トリフルオロメチル－２－チオピリドン

２－クロロ－５－トリフルオロメチルピリジン４グに代えて２,３－ジクロロ－５－トリフルオロメチルピリジン４.７５グを用いる以外は前記合成例２と同様にして反応を行ない、後処理を行なって融点１２５～１２８℃の目的物１９グを得た。

特許出願人　石原産業株式会社

－8完－

UNITED STATES PATENT OFFICE.

HERMANN THOMS, OF BERLIN, GERMANY.

PROCESS OF MAKING PARA-PHENETOL CARBAMIDE.

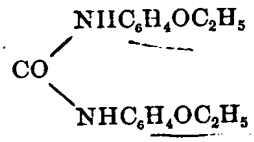
SPECIFICATION forming part of Letters Patent No. 502,504, dated August 1, 1893.

Application filed November 18, 1892. Serial No. 452,446. (Specimens.)

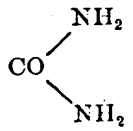
To all whom it may concern:

Be it known that I, HERMANN THOMS, chemist, a subject of the Emperor of Germany, residing in the city of Berlin, German Empire, have invented certain new and useful Improvements in the Production of Para Phenetol Carbamide; and I do hereby declare that the following is a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

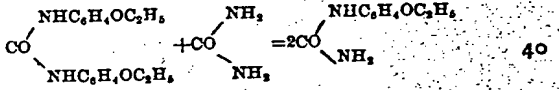
My previous researches (published in the *Pharm. Centralhalle*, March 24, 1892,) have shown that di-para-phenetylurea



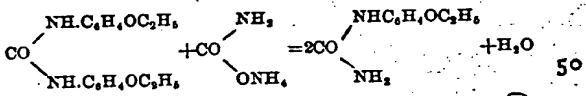
may be readily obtained, in addition to the hydrochlorid of phenetidin, by causing carbonylchlorid to act on a solution of para phenetidin in toluene. Since then I have found that this body, when heated for several hours with common urea



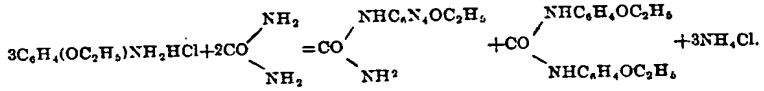
in equimolecular proportions in a closed vessel, and at a temperature ranging between 150° and 160° centigrade, is easily converted into the para phenetol carbamide as indicated by the following equation:—



Instead of the common urea the carbamide salt of ammonia or commercial ammonium carbonate may be employed. The reaction takes place in the first case as indicated by the following equation:



I have found also, that instead of the diparaphenetylurea, paraphenetidin or the hydrochlorid of para-phenetidin may be employed, the latter being either treated in a closed vessel with common urea, or the carbamide salt of ammonia, or with commercial ammonium carbonate at a temperature of 160° centigrade; or an aqueous solution of the hydrochlorid of the paraphenetidin (three molecules) and common urea (two molecules) being heated and kept at the boiling point for a considerable time, the reaction being indicated by the following equation:



This process will yield, in addition to the para-phenetol carbamide, diparaphenetylurea. The paraphenetolcarbamide crystallizes from the hot filtrate.

The paraphenetolcarbamide obtained as described from diparaphenylurea, or from paraphenetidin by the action of common urea or the carbamide salt of ammonia, or commercial ammonium carbonate, melts at a temperature approaching 170° centigrade, and has a sweet taste of extraordinary intensity which renders it suitable for industrial application as a sweetening substance. According to physiological experiments, the new substance is quite harmless to the human organism.

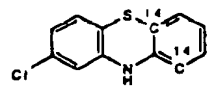
Having thus described my invention, what I claim as new therein, and desire to secure by Letters Patent, is—

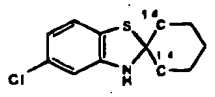
1. The process of obtaining paraphenetol carbamide, by the reaction of a para salt of phenetidin on a substance such as common urea in about the proportions set forth.

2. The process of obtaining para-phenetolcarbamide, which consists in boiling an aqueous solution of para-phenetidin-hydrochlorid with common urea in about the proportions set forth.

HERMANN THOMS.

Witnesses:
FRITZ RINDEL,
AUG. FRAHNE.


I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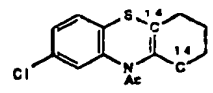
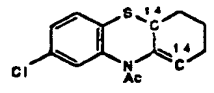
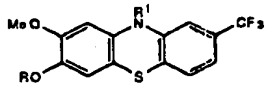
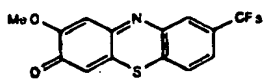

III


IV

to give the tetrahydrophenothiazine olefin mixt. III and IV which was directly converted to labeled I via treatment with DDQ in refluxing benzene followed by hydrolysis of the acetyl group.

91: 74554j **Synthesis of 7,8-disubstituted metabolites of triflupromazine: 2-(trifluoromethyl)-7,8-dimethoxy-10-[3-(dimethylamino)propyl]-phenothiazine and related compounds.** Mital, R. L.; Mittal, Madhu; Laxmi, V.; Mittal, Suresh; Shukla, A. P. (Dep. Chem., Univ. Rajasthan, Jaipur, 302 004 India). *J. Inst. Chem. (India)* 1978, 50(4), 159–61 (Eng). Phenothiazine I [R = Me, R¹ = $(CH_2)_3NMe_2$], a

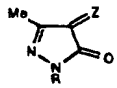

I

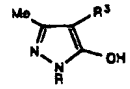

II

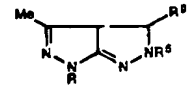
metabolite of triflupromazine was prepd. Thus, condensation of 2,4-$H_2N(F_3C)C_6H_3SH$ Zn salt with 2-chloro-5-methoxy-*p*-benzoquinone in refluxing EtOH 4 h gave II quant., II was reduced with $Na_2S_2O_4$ in aq. Me_2CO to give 90% phenothiazinol I (R = R¹ = H). The product was *O*-methylated with Me_2SO_4 in Me_2CO contg. $Na_2S_2O_4$ and aq. KOH 4h at 60° and the product ether I (R = Me, R¹ = H) (67% yield) was *N*-alkylated by $Cl(CH_2)_3NMe_2$ in Me_2SO contg. NaH 2 h at room temp. to give I [R = Me, R¹ = $(CH_2)_3NMe_2$], characterized as its maleate.

DIAZINES

91: 74555k **Reactions of 3-methyl-1-aryl-Δ²-pyrazolin-5-ones with aromatic aldehydes, aryldiazonium chlorides and of their products 3-methyl-1-aryl-4-arylidene-Δ²-pyrazolin-5-ones with secondary amines, hydrazines, dialkyl phosphites, Grignard reagents, ethyl aceto- or cyanoacetate and cyclohexanone.** Zimaity, T.; Afsah, E.; Abbas, M. (Fac. Sci., Mansoura Univ., Mansoura, Egypt). *Indian J. Chem., Sect. B* 1978, 16B(10), 876–9 (Eng). Reactions of I (R = *p*-ClC_6H_4,

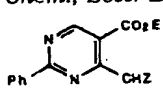

I


IV


V

p-$O_2NC_6H_4$; Z = H_2 (II) with R¹CHO (R¹ = *p*-$MeOC_6H_4$, $O_2NC_6H_4$, $Me_2NC_6H_4$; thienyl) gave I (Z = CHR¹) (III). II and *p*-$ClC_6H_4N_2Cl$ gave I (Z = H, N:NC_6H_4Cl-*p*). Mannich reaction of II gave I (Z = H, R^2NHCH_2; R^2 = *p*-ClC_6H_4, Me). III and piperidine gave IV (R^3 = *p*-$MeOC_6H_4CHR^4$, R^4 = piperidino, etc.). Cyclization of III with N_2H_4 and $PhNHNH_2$ gave V (R^5 = Ph, H; R^6 = *p*-$MeOC_6H_4$ etc.). Reactions of II with dialkyl phosphite, Grignard reagents, Et acetoacetate, $NCCH_2CO_2Et$ and cyclohexanone gave compds. related to I and IV.

91: 74556m **Synthesis and biological activity of α-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinyl)-N-substituted nitrones.** Roy, S. K.; Rao, K. Srinivasa; Reddi, G. S.; Sachdeva, Meena (Res. Dev. Dep., Indian Drugs and Pharm. Ltd., Hyderabad, India). *Indian J. Chem., Sect. B* 1978, 16B(10), 907–9 (Eng).

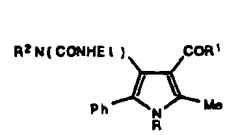


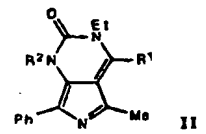
I, Z=N(O)R
III, Z=O
IV, Z=H₂

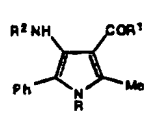
Title compds. I (R = Et, Pr, Bu, CH_2CH_2OH, Ph, $PhCH_2$, *o*-MeC_6H_4, *p*-ClC_6H_4 (II), *p*-$MeSO_2C_6H_4$) were prepd. by treating RNHOH with pyrimidinecarboxaldehyde III, which was prepd. by Kroehnke oxidn. of IV. I at 25–200 μg/mL were fungicidal against dematophytes. II killed *Mycobaterium tuberculosis* at 25 μg/mL.

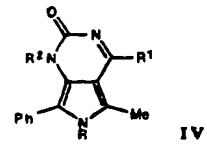
91: 74557n **Pyrimidines. Part LXXVI. tert-Butylation of quinazoline.** De Bie, D. A.; Nagel, A.; Van der Plas, H. C.; Geurtsen, G.; Koudijs, A. (Lab. Org. Chem., Agric. Univ., Wageningen, Neth.). *Tetrahedron Lett.* 1979, (7), 649–52 (Eng). Quinazoline (I) is present in soln. at pH 3 as its cationic covalent hydrate; and treatment of an aq. soln. of I with excess Me_3CCO_2H and ammonium peroxydisulfate, in the presence of a catalytic amt. of $AgNO_3$ at 40° and at pH 1, gave 2-*tert*-butyl-3,4-dihydro-4-oxoquinazoline (II), quant. Similar treatment of I at 70° and at pH 5 for 2 h gave a 4:3:2 mixt. of 2-*tert*-butylquinazoline (III), 4-*tert*-butylquinazoline (IV), and 2,4-di-*tert*-butylquinazoline (V), whereas similar treatment of I at 70° and at pH 4 gave mainly 2-$HCOC_6H_4NHCHO$ and 2-$HCOC_6H_4NH_2$ (VI). At pH 3, VI was the main product together with III, IV, V, and 4-*tert*-butyl-3,4-dihydroquinazoline. The formation of II, III, IV, V, and VI is discussed.

91: 74558p **Synthesis and antiinflammatory properties of some pyrrolo(1H,3H)[3,4-d]pyrimidin-2-ones and pyrrolo(1H,6H)[3,4-d]pyrimidin-2-on s.** Tarzia, G.; Panzone, G.; Schiatti, P.; Selva, D. (Dep. Org. Chem., Lepetit Res. Lab., Milan, Italy). *Farmaco, Ed. Sci.* 1979, 34(4), 316–30 (Eng).


I

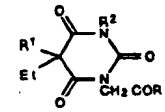

II


III


IV

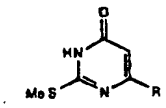
The cyclocondensation reaction of pyrroles I (R = H, Me, Et; R¹ = Me, Ph; R² = Et, H, $CHMe_2$) in MeOH contg. HCl yielded pyrrolopyrimidinones II, and III (R, R¹, and R² same as above), which reacted with NaOCN at room temp. to give IV; II and IV exhibited antiinflammatory activity. III (R = R² = Et, R¹ = Me) in HOAc was added to NaOCN in H_2O, and the mixt. was kept 4 h at room temp. to give IV (R = R² = Et, R¹ = Me).

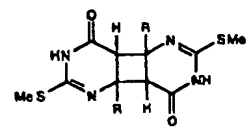
91: 74559q **Synthesis and pharmacological screening of some N-carboxymethylbarbituric acid derivatives. I.** Mirek, Julian; Adamczyk, Maciej; Chojnacka-Wojcik, Ewa; Naparzewska, Anna (Inst. Chem., Jagellonian Univ., 30-060 Krakow, Pol.). *Pol. J. Pharmacol. Pharm.* 1978, 30(5), 685–93 (Eng). Methylphenobarbital or barbital were *N*-alkylated with

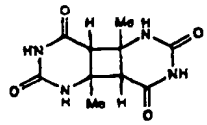

I

$ClCH_2CO_2Me$ or $BrCH_2CO_2Et$ in PhMe contg. K_2CO_3 to give 87–90% carbalkoxy derivs. I (R = OMe, OEt, R¹ = Ph, R² = Me) or 85–6% I (R = OMe, R² = CH_2CO_2Me, R = OEt, R² = CH_2CO_2Et, R¹ = Et). Hydrolysis of these esters with refluxing concd. HCl gave 90% I (R = OH, R¹ = Ph, R² = Me) or 95% I (R = OH, R¹ = Et, R² = CH_2CO_2H) which were converted into 95% the corresponding acid chlorides with $SOCl_2$. I (R = Cl, R¹ = Ph, R² = Me) was treated with 2 mol-equiv amines to give 82–90% amides I (R = 2-, 4-$HO_2CC_6H_4NH$, 3-pyridylamino, 4-pyridylmethylamino). I (R = Cl, R¹ = Et, R² = CH_2COCl) was treated with 4 mol-equiv amines to give 89–92% diamides I (R = 2-, 4-$HO_2CC_6H_4NH$, 3-pyridylamino, 4-pyridylmethylamino, morpholino; R¹ = $RCOCH_2$). The amides had no anticonvulsant activity and showed only slight sedative and analgesic action.

91: 74560h **Photolysis of thiopyrimidine derivatives. Part II. 2-(Methylthio)-6-methyluracil and 2-(methylthi)-6-ethyluracil.** Golankiewicz, Krzysztof; Szajda, Maria; Wyrzykiewicz, Elzbieta (Inst. Chem., A. Mickiewicz Univ., 60780 Poznan, Pol.). *Pol. J. Chem.* 1979, 53(2), 529–31 (Eng). Irradn. of I (R = Me,


I


II


III

Et) in Me_2CO at λ >254 nm gives 20.5% II (R = Me, Et); irradn. of aq. II at 254 nm gave I. The hydrolysis of II (R = Me) gave III which on irradn. (in acidic, basic, or neutral H_2O) at 254 nm gave 6-methyluracil; this established the anti-configuration for II (R = Me). The photodimerization of I (R = alkyl) was contrasted to the lack of photodimerization of I (R = CO_2H).

91: 74561j **Succinat dehydrogenase inhibitory activity of new 1-aryl-3-(N,N-dimethylaminopropyl) thiobarbiturates.** Tripathi, Shephali; Pandey, B. R.; Raman, K.; Barthwal, J. P.; Kisher, K.; Bhargava, K. P. (King Georg's Med. Coll., Lucknow Univ., Lucknow, India). *Eur. J. Med. Chem. - Chim. Ther.* 1979, 14(2), 133–4 (Eng). Thiobarbiturates I (R = Ph, isomeric tolyl, xylyl, or anisyl, 2-$EtOC_6H_4$, 2- or 4-ClC_6H_4, 4-BrC_6H_4) were prepd. by treating $Me_2NCH_2CH_2CH_2NH_2$ with RNCS and cyclocondensing product thioureas $Me_2NCH_2CH_2CH_2NHC(S)NHR$ with malonic acid. I inhibited (15.1–75.50%) succinate dehydrogenase in vitro activity of rat brain homogenate.